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10/694,634	10/27/2003	Jun Tan	4303-032029	2636

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EXAMINER	
POPA, ILEANA	

ART UNIT	PAPER NUMBER
1633	

DATE MAILED: 11/28/2006

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/694,634	TAN ET AL.	
	Examiner	Art Unit	
	Ileana Popa	1633	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *29 September 2006*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-92* is/are pending in the application.

4a) Of the above claim(s) *5-7,9-15,17,18 and 21-92* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-4,8,16,19 and 20* is/are rejected.

7)☒ Claim(s) *20* is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *27 October 2003* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Election/Restrictions

1. Applicant's election without traverse of the invention of Group I, drawn to a research model for screening compounds suspected of modulating CD40L/CD40R signaling pathway, and of species of animal, central nervous system cells, tumor necrosis factor, compounds that bind CD40L, and neuroinflammation, in the reply filed on 09/29/2006 is acknowledged.

Claims 5-7, 9-15, 17, 18, and 21-92 have been withdrawn from further consideration pursuant to 37 CFR 1.142(b) as being drawn to a nonelected inventions or species, there being no allowable generic or linking claim.

Claims 1-4, 8, 16, 19, and 20 are under examination.

Claim Objections

2. Claim 20 is objected to because of the following informalities: claim 20 recites "trangsegenic presenilin" and "trangenic DC40L". Appropriate correction to "transgenic presenilin" and "transgenic DC40L" is required.

Double Patenting

3. The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees.

A nonstatutory obviousness-type double patenting rejection is appropriate where the conflicting claims are not identical, but at least one examined

application claim is not patentably distinct from the reference claim(s) because the examined application claim is either anticipated by, or would have been obvious over, the reference claim(s). See, e.g., *In re Berg*, 140 F.3d 1428, 46 USPQ2d 1226 (Fed. Cir. 1998); *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970); and *In re Thorington*, 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) or 1.321(d) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent either is shown to be commonly owned with this application, or claims an invention made as a result of activities undertaken within the scope of a joint research agreement.

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

4. Claims 1-4, 8, 16, 19, and 20 are rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claim 8 of U.S. Patent No. 6,787,318, as evidenced by Tan et al. (Science, 1999, 286: 2352-2355). Although the conflicting claims are not identical, they are not patentably distinct from each other because they are obvious variants.

The instant claims are drawn to a research model for screening compounds suspected of modulating CD40L/CD40R signaling pathway in an animal by contacting a first sample of cells with CD40L and measuring the level of a marker, contacting a second sample of cells with a compound and CD40L and measuring the level of a marker, and comparing the level of the marker in the first sample of cells with the level of the marker in the second sample of cells (claim 1). The cell samples can be derived from cells of the central nervous system (claim 2), the marker is a cytokine such as tumor necrosis factor (TNF) (claims 3 and 4), the compound can be an agent that binds

to CD40L (claim 8), the animal is afflicted with a disease that can be neuronal inflammation (claim 16), and the animal can be a non-transgenic animal or transgenic animal over-expressing APP (claims 19 and 20). The specification discloses that the screening method is performed *in vitro* (p. 3, paragraphs 0015 and 0016).

The patent claim 8 recites a method of determining therapeutic effectiveness (i.e., screening) of an agent for Alzheimer's disease (i.e., neuronal inflammation) by measuring *in vitro* inhibition of the CD40/CD40L binding in the presence of the agent and correlating any increase in inhibition to an increase in effectiveness of the agent for Alzheimer's disease, followed by measuring the agent's effectiveness in reducing Alzheimer's disease pathology. The specification discloses that the assay includes the steps of treating microglial cells (i.e., cells of the central nervous system) with APP, adding CD40L to the microglial cells, adding an agent to the microglial cells, and measuring the Alzheimer's disease pathology (column 7, lines 14-20). The specification also discloses that Alzheimer's disease pathology is measured by determining the amount of TNF production following microglial activation by APP (column 5, lines 55-65) and that the agent can be an antibody or other compounds that block the binding of CD40L to CD40 (i.e., the agent can be an antibody that binds CD40L) (column 5, lines 45-54). With respect of the limitation of the cells being derived from a transgenic animal over-expressing APP, one of skill in the art would have had known to use such as an alternative because the specification teaches that microglia isolated from these transgenic animals express markedly increased amounts of CD40, as compared to microglia isolated from control animals (column 15, lines 10-19). With respect to the

limitation of comparing the results with a control represented by cells treated with CD40, as recited in the instant claim 1, one of skill in the art would have known to use such because using such controls are routine in the art (see Tan et al., p. 2353, column 1, second paragraph and Web. Fig. 4). Therefore, the patented claim 8 anticipates claims 1-4 8, 16, 19, and 20 of the instant application. Since the patent claim embraces all the limitation of the instant claims, the patent claim and the application claims are obvious variants of one another.

5. Claims 1-4, 8, and 19 are rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 1, 2, 4, 5, 11, and 12 of the copending Application No.11/523,468. Although the conflicting claims are not identical, they are not patentably distinct from each other because they are obvious variants.

Claims 1-4, 8, and 19 are claiming the same invention as that of claims 1, 2, 4, 5, 11, and 12 of copending Application No. 11/523,468, with the exception that the instant claims recite screening for compounds suspected of modulating CD40L/CD40R signaling pathway, whereas the copending application recites screening for compounds that modulate CD40L/CD40R, which are encompassed by the suspected modulators of the instant application.

This is a provisional double patenting rejection since the conflicting claims have not in fact been patented.

Claim Rejections - 35 USC § 112, 2nd paragraph

7. The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter that the applicant regards as his invention.

8. Claim 1 is rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

It is not clear, from the language of the claim, whether the marker for the cells contacted with the CD40 ligand is the same as that for the cells contacted with the CD40 ligand and the compound. Therefore, the metes and bounds of the claim cannot be determined and the claim is indefinite.

Claims 2-4, 8, 16, 19, and 20 are rejected for being dependent from the rejected claim 1.

9. Claim 1 is rejected under 35 U.S.C. 112, second paragraph, as being incomplete for omitting essential steps, such omission amounting to a gap between the steps. See MPEP § 2172.01. The omitted steps are: the step reciting that the comparison between the first and second sample leads to the identification of a compound that is suspected of modulating CD40L/CD40R signaling pathway.

** It is noted that claim 1 is interpreted as being drawn to a method of screening, and not to a research model.

Claims 2-4, 8, 16, 19, and 20 are rejected for being dependent from the rejected claim 1.

10. Claims 2-4, 8, 16, 19, and 20 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claims 2-4, 8, 16, 19, and 20 recite the limitation "the method of claim 1". There is insufficient antecedent basis for this limitation in the claim, because it is unclear if claim 1 is drawn to a method.

11. Claims 2, 8, and 16 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

A broad range or limitation together with a narrow range or limitation that falls within the broad range or limitation (in the same claim) is considered indefinite, since the resulting claim does not clearly set forth the metes and bounds of the patent protection desired. See MPEP § 2173.05(c). Note the explanation given by the Board of Patent Appeals and Interferences in *Ex parte Wu*, 10 USPQ2d 2031, 2033 (Bd. Pat. App. & Inter. 1989), as to where broad language is followed by "such as" and then narrow language. The Board stated that this can render a claim indefinite by raising a question or doubt as to whether the feature introduced by such language is (a) merely exemplary of the remainder of the claim, and therefore not required, or (b) a required feature of the claims. Note also, for example, the decisions of *Ex parte Steigewald*, 131 USPQ 74 (Bd. App. 1961); *Ex parte Hall*, 83 USPQ 38 (Bd. App. 1948); and *Ex parte Hasche*, 86 USPQ 481 (Bd. App. 1949).

Claim 2 recites the broad recitations "central nervous system cells", "peripheral cells", "transgenic cells", and "human cells", and the claim also recites "cell lines derived from central nervous system", "cell lines derived from peripheral cells", "transgenic cells derived from transgenic animals", and "immortalized or non-immortalized cell lines derived from humans", respectively, which are the narrower statements of the ranges/limitations. It is noted that: (i) the broad recitations of central nervous system cells, peripheral cells or human cells encompass cells within the animal, primary cell cultures, and established cell lines, (ii) the broad recitation of transgenic cells encompasses cells transfected or transduced *in vitro*, transgenic cells derived from transgenic animals, and also immortalized cells. Similarly, the claim recites: (i) the broad limitation of human cells that encompasses the narrower limitations of central nervous system cells, peripheral cells, or even transgenic cells obtained *in vitro* by transfection or transduction, (ii) the broad limitations of non-immortalized cell lines derived from humans, higher primate, primate, and murine sources that encompass central nervous system and peripheral cell lines, and (iii) the broad limitation of humans cell lines that encompasses the limitations of "immortalized or non-immortalized cell lines derived from humans".

Claim 8 recites: (i) the broad limitation of "a compound that modulates the CD40L/CD40R signaling pathway upstream or downstream of CD40L/CD40R interaction", and the claim also recites " a compound that binds to CD40R", "a compound that binds to CD40L", or "a compound that interferes with TNF receptor-

associated factors", which are the narrower statements of the ranges/limitations, (ii) the broad limitation of "a compound that reduces β-amyloid burden", and also a compound that interferes with presenilin-1 or presenilin-2, a compound that inhibits the activity of β- or γ secretase, a compound that enhances the activity of α-secretase, a compound that alters APP processing, a compound that reduces the ratio of APP β-CTF to APP α-CTF, a compound that reduces the amount of APP β-CTF, a compound that promotes brain-to-blood clearance of β-amyloid, a compound that increases circulating levels of β-amyloid, a compound that reduces the size and number of amyloid plaques, a compound that reduces total β-amyloid levels, or a compound that reduces congophilic β-amyloid deposits, which are the narrower statements of the ranges/limitations, and (iii) the broad limitation of "an immunogenic CD40L compound", and also a soluble CD40L compound, or a soluble CD40L variant, which are the narrower statements of the ranges/limitations. Similarly, the claim also recites the broad limitation of "a compound that binds CD40L" that encompasses a compound that decreases trimerization of CD40L, agonistic or antagonistic antibodies to CD40L, and the broad limitation of "a compound that binds CD40LR" that encompasses a compound that decreases trimerization of CD40R, agonistic or antagonistic antibodies to CD40R.

Claim 16 recites the broad limitations of "neuronal inflammation" and the claim also recites "tauopathy", amyloidogenic disease", which are the narrower statements of the ranges/limitations. The claim also recites the broader limitation of "brain trauma", followed by the narrower range "brain injury".

12. Claim 1 is rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

The preamble of claim 1 recites a research model (i.e., a composition), whereas the body of the claim recites method steps. Since it is not clear whether the claim is drawn to a composition or a method, the metes and bounds of the claim cannot be determined, and the claim is indefinite.

Claims 2-4, 8, 16, 19, and 20 are rejected for being dependent from the indefinite claim 1.

13. Claims 1-4, 8, and 19 are rejected under 35 U.S.C. 112, second paragraph, as being incomplete for omitting essential elements, such omission amounting to a gap between the elements. See MPEP § 2172.01.

The instant claims recite "interfering with the CD40L/CD40R signaling pathway in an animal" comprising contacting cell with CD40 ligand. However, screening for such a modulator requires the presence of CD40R on cells and the claims do not recite this.

Claim Rejections - 35 USC § 102

14. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

(e) the invention was described in (1) an application for patent, published under section 122(b), by another filed in the United States before the invention by the applicant for patent or (2) a patent granted on an application for patent by another filed in the United States before the invention by the applicant for patent, except that an international application filed under the treaty defined in section 351(a) shall have the effects for purposes of this subsection of an application filed in the United States only if the international application designated the United States and was published under Article 21(2) of such treaty in the English language.

15. Claims 1-4 are rejected under 35 U.S.C. 102(b) as being anticipated by Tan et al.

** The rejection of claim 1 is based on the interpretation that the claim is drawn to a method of screening.

Tan et al. teach a method for testing the ability of monoclonal antibodies directed against CD40R to interfere with the CD40L/CD40R signaling pathway after treatment with $A\beta_{1-42}$ (it is noted that treatment with $A\beta_{1-42}$ is used to induce expression of CD40R on microglia, which otherwise do not express or express very low amounts of CD40R), the method comprising: (i) contacting a first sample of microglial cells (i.e., central nervous system cells) with CD49L and measuring the level of the produced TNF-α, (ii) contacting a second sample of microglial cells with $A\beta_{1-42}$ and CD40L, and measuring the level of the produced TNF-α, and (iii) comparing the level of TNF-α in the first sample with the level of TNF-α in the second sample (p. 2353, columns 1 and 2 ; the also the attached Web Fig. 4). Since Tan et al. teach all the limitations of the instant claims, the claimed invention is anticipated by the above-cited art.

16. Claim 1 is rejected under 35 U.S.C. 102(e) as being anticipated by Force et al. (PGPUB 2003/0059427).

Force et al. teach a method of screening the ability of antibodies directed against CD40R to interfere with the CD40L/CD40R signaling pathway by contacting cells that

express CD49R with the antibodies to be tested in the absence or presence of CD49L and measuring the level of CD95 expression (i.e., measuring the level of a marker) (p. 3, paragraph 0029, p. 117, paragraph 0176, and Fig. 3). Since Force et al. teach a method of screening the ability of compounds to interfere with the CD40L/CD40R signaling pathway by (i) contacting a first sample of cells with CD49L and measuring the level of a marker, (ii) contacting a second sample of cells with a compound and CD40L, and measuring the level of the same marker, and (iii) comparing the level of the marker in the first sample with the level of the same marker in the second sample, the claimed invention is anticipated by the above-cited art.

Claim Rejections - 35 USC § 103

17. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

18. Claims 1-4, 8, 16, 19, and 20 are rejected under 35 U.S.C. 103(a) as being unpatentable over either Tan et al., as applied to claims 1-4, in view of both Zheng et al. (PGPUB 2004/0067982) and Gerritse et al. (Proc Natl Acad Sci USA, 1996, 93: 2499-2504).

** The rejection of claim 1 is based on the interpretation that the claim is drawn to a method of screening.

Tan et al. do not teach a compound that binds CD40L (claim 8). Tan et al. teach that microglia isolated from Tg APP_{SW} transgenic mice (used as models for Alzheimer's disease) express CD40R, however, they do not teach using these mice or cells derived from them in their method of screening (claim 20) (p. 2352, column 2). Zheng et al. teach novel compounds that bind CD40L and screening these compounds for the ability of interfering with the CD40L/CD40R signaling pathway (p. 2, paragraphs 0009, 0012, and 0013, p. 9., paragraph 0095). Zheng et al. also teach that these compounds can be used to inhibit CD40L/CD40R signaling pathway in animals (for example mice) affected with diseases such as Alzheimer's disease (i.e., a neuronal inflammation disorder, see Tan et al.), as recited in claims 16 and 19 (p. 9, paragraphs 0099 and 0101). It would have been obvious to one of skill in the art, at the time the invention was made, to use the method of Tan et al. to screen the compounds of Zheng et al. for their ability interfere with the CD40L/CD40R signaling pathway, with a reasonable expectation of success. The motivation to do so is provided by Gerritse et al., who teach that CD40L has advantages over the constitutively expressed CD40R as a target for intervention because its transient expression is restricted to $CD4^+$ T cells, which allows targeting only the T cells actively participating in the response, without affecting the population of T cells at large (p. 2504, column 1). One of skill in the art would have been expected to have a reasonable expectation of success in using such a method because the art teaches the successful use of this method to identify compounds with the ability of modulating the CD40L/CD40R signaling pathway. One of skill in the art would have known to also use the method of Tan et al. with microglia isolated from Tg APP_{SW}

transgenic mice, because Tan et al. teach that these cells express high amounts of CD40R. Thus, the claimed invention was *prima facie* obvious at the time the invention was made.

19. Claims 1, 8, 16, and 19 are rejected under 35 U.S.C. 103(a) as being unpatentable over Force et al., as applied to claim 1 above, in view of both Zheng et al. and Gerritse et al.

** The rejection of claim 1 is based on the interpretation that the claim is drawn to a method of screening.

Force et al. do not teach a compound that binds CD40L (claim 8). Zheng et al. teach novel compounds that bind CD40L and screening these compounds for the ability of interfering with the CD40L/CD40R signaling pathway (p. 2, paragraphs 0009, 0012, and 0013, p. 9., paragraph 0095). Zheng et al. also teach that these compounds can be used to inhibit CD40L/CD40R signaling pathway in animals (for example mice) affected with diseases such as Alzheimer's disease (i.e., a neuronal inflammation disorder, see Tan et al.), as recited in claims 16 and 19 (p. 9, paragraphs 0099 and 0101). It would have been obvious to one of skill in the art, at the time the invention was made, to use the method of Force et al. to screen the compounds of Zheng et al. for their ability interfere with the CD40L/CD40R signaling pathway, with a reasonable expectation of success. The motivation to do so is provided by Gerritse et al., who teach that CD40L has advantages over the constitutively expressed CD40R as a target for intervention because its transient expression is restricted to $CD4^+$ T cells, which allows targeting

only the T cells actively participating in the response, without affecting the population of T cells at large (p. 2504, column 1). One of skill in the art would have been expected to have a reasonable expectation of success in using such a method because the art teaches the successful use of this method to identify compounds with the ability of modulating the CD40L/CD40R signaling pathway. Thus, the claimed invention was *prima facie* obvious at the time the invention was made.

20. No claim is allowed. No claim is free of prior art.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Ileana Popa whose telephone number is 571-272-5546. The examiner can normally be reached on 9:00 am-5:30 pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Joseph Woitach can be reached at 571-272-0739. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

Ileana Popa, PhD

JANET L. EPPS-FORD, PH.D.
PRIMARY EXAMINER